UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,661	03/26/2001	Jane Osbourn	84633-000100US	9792

24197 7590 11/17/2004

KLARQUIST SPARKMAN, LLP
121 SW SALMON STREET
SUITE 1600
PORTLAND, OR 97204

EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/817,661	OSBOURN ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *2-7,15-20 and 24-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8-14 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/4 1/6 10/7 12/6*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Receipt is acknowledged of a Response to a Restriction Requirement, which was dated on June 25, 2003 (e.g., see exhibit B in 8/27/04 Response).

Status of the Claims

2. Claims 1-30 are pending in the present application.

3. Applicant's response to the Restriction and/or Election of Species requirements in Paper No. 4 is acknowledged (Applicant elected ***with traverse*** Group I, claims 1-14 and 21-23) and claims 15-20 and 24-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

4. Please note: Applicant's elected species (Subgroup 1 =antibody; Subgroup 2 = mRNA not containing a midvariant (MDV), not containing a glycine-serine tether and containing a TMV encapsidation sequence; Subgroup 3 = TMV coat protein; Subgroups 4-5 = RT-PCR; Subgroup 6 = prokaryotic ribosome; Subgroup 7 = no glutathione; Subgroup 8 = disulphide isomerase added; Subgroup 9 = heparin added; Subgroup 10 = mutagenic oligonucleotides and PCR) was found in the art. See MPEP § 803.02 (emphasis added):

> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be

rejected and claims to the nonelected species held withdrawn from further consideration. ***The prior art search, however, will not be extended unnecessarily to cover all nonelected species***. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

5. Claims 2-7 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species, the requirement having been traversed in Paper No. 6 (see below i.e., ***Response to Restriction and/or Election of Species***).

6. Therefore, claims 1, 8-14 and 21-23 are examined on the merits in this action.

Response to Restriction and/or Election of Species

7. Applicant's election of Group I (claims 1-14 and 21-23) **with traverse** is acknowledged.

8. The traversal is on the ground(s) that (a) "All of claims 1 to 24 fully incorporate claim 1, so that a complete search of claim 1 will as a necessity encompass fully the subject-matter of all of claims 1 to 24. Furthermore, all of claims 25 to 30 fully incorporate claim 25, so that a complete search of claim 25 will as a necessity encompass fully the subject matter of all of claims 25 to 30. Claims 1 and 25 contain corresponding technical features" (e.g., see exhibit B, page 4, first full paragraph) and (b) "A thorough search of the patent or scientific literature directed to such methods and to uses thereof would encompass art in the field of the invention as claimed. For example, a thorough search encompassing the claims of Group I would encompass

art in the field of Group II, all of which claims depend from claim 1. Further, Applicants believe a thorough search encompassing the claims of Group I would encompass art in the field of Groups III-IV. Thus, prosecution of the invention, as a whole, would not place a burden on the Examiner" (e.g., see exhibit B, page 4, paragraph 2).

9. These arguments were fully considered but were not found persuasive.

(a) Applicants appear to be arguing for a per se rule prohibiting restriction of patentably distinct subject matter as long as that patentably distinct subject matter is written in a "dependent" form. The Examiner is unaware of any such rule and further contends that such a proposition is inconsistent with the requirements set forth in the MPEP. As noted by Applicants, there are two criteria for a proper restriction between patentably distinct inventions:

> (A) The inventions must be independent or distinct as claimed: and
> (B) There must be a serious burden on the Examiner if restriction is required.

Thus, it does not matter for purposes of restriction whether the claims are written in an "independent" or "dependent" form as long as the restriction requirements (A) and (B) set forth in MPEP § 803 are met. Here, both requirements are met because as stated in the Restriction Requirement dated 2/25/2003, these inventions (Groups I-V) have acquired a separate status in the art as shown by their different classification (e.g., see 2/25/03 Restriction, paragraph 1) and/or divergent subject matter (e.g., see 2/25/03 Restriction, paragraphs 2-7). Furthermore, the different methods and/or products would require completely different searches in both the patent and non-patent databases, and there is no expectation that the searches would be coextensive. Therefore, this does create an undue search burden for the Office.

(b) The mere presence of any alleged overlapping subject matter would not constitute a coextensive search because each Group would have to be searched to its full extent and not just to the extent of any overlapping subject matter, which would, as a practical matter, encompass non-overlapping subject matter and hence result in a non-coextensive search and thus a burden on the Office.

10. Applicant's election of species ***with traverse*** in Exhibit B (e.g., see 8/27/04 Response) is also acknowledged.

11. The election of species traversal is on the ground(s) that (a) "the designation of species is complex and does not appear to be organized along a particular search strategy" (e.g., see exhibit B, page 5, paragraph 2; see also paragraph bridging pages 6-7), (b) "For the Examiner to require election of species among features that are not relevant for patentability and from which a person of ordinary skill can select as of choice is to provide an undue burden on the Applicants, and indeed on the Examiner. Rather, there is no burden in searching across the breadth of the various species that the Examiner seeks election between" (e.g., see exhibit B, page 5, paragraph 3), (c) "The Examiner is seeking to divide a straightforward biotechnological invention into multiple species and sub-species is creating the potential for a multiplication of cost and complexity of searching where in fact a single search relating to the features that actually make up the contribution provided by the invention will be fully adequate (e.g., see exhibit B, paragraph bridging pages 5-6), (d) "the Examiner appears to have designated all identified species as patentably distinct and placed the burden on Applicants to demonstrate otherwise. This is,

respectfully, an improper shifting of the burden" (e.g., see exhibit B, page 6, first full paragraph), (e) "The designation of species also does not appear to be proper because the designated species do not appear to be restricted to those with mutually exclusive characteristics" (e.g., see exhibit B, page 6, paragraphs 2-3) and (f) "Subgroups 7, 8 and 9, The Examiner appears to believe the species within these Subgroups are patentably distinct, but the Examiner has not provided any reasoning to support the assertion" (e.g., see exhibit B, page 6, paragraph 4).

12. These arguments were fully considered but were not found persuasive.

(a) The examiner's position is that no "organizational search strategy" is required in the MPEP and, as a result, Applicants' arguments are moot.

(b) The species are distinct, each from the other, because the structures and modes of action of each of the species encompassed are different as set forth in the original restriction requirement. They would also differ in their reactivity and/or mechanism and/or the products made. Therefore, the species have different issues regarding patentability and represent patentably distinct subject matter. For example, the species of "specific binding pairs" (i.e., Subgroup 1) differ in their structure and function and are also classified separately (e.g., see page 19, lines 11-19, "In preferred embodiments, the specific binding members for display on the ribosomes are antibody molecules ... receptors, enzymes, peptides and protein ligands). Antibodies are classified in class 424, subclass 130.1+ whereas enzymes are classified in class 424, subclass 94.1+"). Likewise, the species of nucleic acid (e.g., subgroup 2) can also be separately classified depending on the nature of the molecule (class 536, subclasses 23.1, 23.53, 24.1, 24.2, etc.) as well as the coat protein for subgroup 3 (e.g., class 530, subclasses 300+, 350+

and class 424, subclass 192.1+, etc.). The species of replication in subgroups 4 and 5 represent divergent subject matter because different reagents and or method steps can be employed (e.g., cloning versus PCR), which can also be separately classified (e.g., class 435, subclass 141.1 versus class 435, subclass 91.2+, respectively). For subgroup 6, the ribosomes represent divergent subject matter because prokaryotic and eukaryotic ribosomes have different structures (e.g., 80S for eukaryotic versus 70S for prokaryotic). For subgroups 7-9, the species represent patentably distinct subject matter because as noted in the original rejection different reagents and/or method steps are e.g., glutathione, PDI, heparin are required in some method steps, but not others). Finally, there are many ways to mutate a protein (e.g., light, chemical, mutagenic PCR etc) all of which require different method steps and/or reagents. Thus, the different species would require different searches and there is no expectation that the searches would be coextensive. The examiner maintains that this does create an undue search burden.

Furthermore, the Examiner previously stated that should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. This has not been done.

(c) No such concern is warranted here because as Applicants have already noted "even if the election of species requirement is maintained then once a generic claim is found to be allowable, ***additional species will be rejoined by the Examiner*** to preserve Applicants' right to claim their invention they require to adequately protect their invention" (e.g., see exhibit B, page 5, paragraph 1), which is in accordance with MPEP § 809.02.

(d) No burden has been shifted because the Examiner has set forth reasons why the species are patentably distinct (e.g., see 2/25/03 Response, pages 5-11) and has further provided separate classifications for each of the species where possible (see section (b) above).

(e) Mutually exclusive properties must be present because claims 2-7 do not read on Applicants' claimed species (e.g., see exhibit B, page 2).

(f) The rationale for subgroups 7-8 was provided in the original restriction and has been further expounded upon above in section (b).

13. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

14. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98 (b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on the form PTO-892, they have not been considered.

15. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action.

Specification

16. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 1, 8-14 and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluckthun et al. (WO 98/48008) (Date of Patent is **October 19, 1998**) (IDS AC) and Dubois et al. (WO 98/00547) (Date of Patent is **January 8, 1998**) (IDS BA) and Landt et al. (Landt, O.; Grunert, H.-P.; Hahn, U. "A general method for rapid site-directed mutagenesis using the polymerase chain reaction" *Gene* **1990**, *96*, 125-128).

For ***claim 1***, Pluckthun et al. (see entire document) teach ribosome display (e.g., see abstract and figure 1), which reads on steps (a)-(c) of claim 1. For example, Pluckthun et al. disclose **(a)** providing mRNA molecules that lack in-frame stop codons (e.g., see figure 1, step 1; see also page 3, last paragraph, "Accordingly, the present invention relates ... (a) translating a population of mRNA molecules devoid of stop codons"). Pluckthun et al. also disclose **(b)** incubating the mRNA molecules under conditions for ribosome translation of the mRNA molecules to produce encoded specific binding pair member, whereby complexes each comprise ribosome, mRNA and encoded specific binding pair member (e.g., see figure 1, step 2). Pluckthun et al. further disclose **(c)** bringing the complexes into contact with the complementary sbp member of interest, and selecting one or more complexes displaying specific binding pair member able to bind the complementary sbp member of interest under the conditions of the selection (e.g., see figure 1, steps 3 and 4). Pluckthun et al. also disclose both prokaryotic and

eukaryotic ribosome display systems (e.g., see bottom of page 8, "Preferably, the translation is carried out in a prokaryotic translation system ... Alternatively, the translation system may be carried out in a eukaryotic translation system").

For ***claim 8***, Pluckthun et al. teach the use of heparin (e.g., see page 11, last paragraph, "In a most preferred embodiment, said blocking compound is ... heparin. Heparin has been suggested to be included as RNase inhibitor (WO 91/05058), but it has surprisingly been found in accordance with the present invention that it additionally decreases non-specific binding").

For ***claim 11***, Pluckthun et al. teach retrieving mRNA from a complex selected in step (c) (e.g., see figure 1, step 5).

For ***claim 12***, Pluckthun et al. teach amplifying and copying the retrieved mRNA into DNA (e.g., see figure 1, step 6; see also page 9, first full paragraph, "The amplification of cDNA, preferably by PCR, with or without subsequent cloning into a suitable vector, further significantly facilitates the identification of the desired nucleic acid molecule"; see especially bottom of page 8, "In a further preferred embodiment of the method of the present invention step (d) comprises (da) reverse transcribing said mRNA; (db) optionally amplifying the resulting cDNA").

For ***claims 13 and 22***, Pluckthun et al. teach the use of *in vitro* expression systems (e.g., see page 3, last paragraph, "Accordingly, the present invention relates to a method for identifying a nucleic acid molecule encoding a (poly)peptide that interacts with a target molecule comprising the following steps: (a) translating a population of mRNA

molecules devoid of stop codons in the correct reading frame in an in vitro translation system").

For ***claims 14 and 23***, Pluckthun et al. disclose isolating and purifying the product (e.g., see figure 1, steps 4 and 5; see also example 7).

The prior art teachings of Pluckthun et al. differ from the claimed invention as follows:

For ***claim 1***, Pluckthun et al. are deficient in that they do not specifically teach the use of "encapsidation" to protect the mRNA in a viral coat protein. Pluckthun et al. only teach the use of stem-loop sequences and ribonuclease inhibitors like vanadyl ribonuclease complexes (e.g., see Pluckthun et al., example 8; see also bottom of page 7).

For ***claims 9 and 21***, Pluckthun et al. are deficient in that they do not explicitly teach the use of "mutagenic primers" in RT-PCR. Pluckthun et al. only teach the use of RT-PCR for the purposes of mutagenizing the cDNA library, but they do not state how they do it i.e., "mutagenic primers" are never mentioned (e.g., see page 4, paragraph 4, "The population of mRNA molecules may be of varying origin. For example, it may be derived from a cDNA library ... Particularly advantageous is also the use of the present invention in mutagenized (poly)peptides to find improved variants"; see also example 7, "Thus, the selective pressure to maintain antigen binding, executed by binding and elution from immobilized antigen is clearly operating, albeit in the context of an ongoing genetic diversification through PCR errors").

For ***claim 10***, Pluckthun et al. do not teach the use of tobacco mosaic virus.

However, Dubois et al. teach the following limitations that are deficient in Pluckthun et al.:

For ***claim 1***, Dubois et al. (see entire document) teach the use of in vitro encapsidation using viral coat proteins to protect labile mRNA (e.g., see Dubois et al., Summary of Invention; see also page 10, lines 17-28; see also claims 3 and 4).

For ***claims 9 and 21***, Landt et al. teach the use of "mutagneic primers" as a "general and rapid method for site-directed mutagenesis" (e.g., see Landt et al., abstract).

For ***claim 10***, Dubois et al. teach the use of tobacco mosaic virus (e.g., see Dubois et al., claim 16).

It would have been obvious to one skilled in the art at the time the invention was made to protect the nuclease labile mRNA as taught by Pluckthun et al. in their ribosome display experiments with viral coat proteins as taught by Dubois et al. because Pluckthun et al. state that their mRNA are susceptible to nuclease digestion and Dubois et al. state that they have a method for protecting mRNA from this type of digestion via viral coat protein encapsidation (e.g., see Pluckthun et al., example 8; see also bottom of page 7 wherein stem-loops and vanadyl inhibitors are used to protect the mRNA from nuclease digestion; see also Dubois et al., abstract; see also page 10, lines 17-28; see also page 3, paragraph 2, "RNA bacteriophages have long been used as model systems to study the mechanisms of RNA replication and translation. The RNA genome within RNA bacteriophages is resistant to ribonuclease digestion due to the protein coat of the bacteriophage"). Furthermore, one of ordinary skill in the art would have been motivated to use the viral coat protein taught by Dubois et al. to replace and/or add to the stem-

loop/vanadyl inhibitor protection because this viral coat protein would not inhibit the protein synthesis that is required during the translation process as does the vanadyl ribonuclease inhibitors described by Pluckthun et al. (e.g., see Pluckthun et al., example 5, "Nucleases were found to be efficiently inhibited by vanadyl ribonucleoside complexes ... even though protein synthesis was partially inhibited"). In addition, Dubois et al. state, "ArmoredRNA withstands plasma/serum nucleases very well compared to naked RNA" (e.g., see page 36, second to last paragraph) and also that the viral coat proteins are easy to group and purify in many cases (e.g., see page 3, paragraph 2, "Bacteriophage are simple to grow and purify, and the genomic RNA is easy to purify from the bacteriophages"). Finally, one of ordinary skill in the art would have reasonably expected to be successful because Dubois et al. teach that their viral coat protein encapsidation method can be use for in vitro expression systems (see Dubois et al., page 11, paragraph 1, "The non-bacteriophage RNA may be used ... for transient gene expression in vitro and in vivo"), which would encompass the in vitro expression systems of Pluckthun et al.

Furthermore, it would have been obvious to one skilled in the art at the time the invention was made to employ the "mutagenic primers" as taught by Landt et al. in the ribosome display as taught by Pluckthun et al. because a preferred embodiment of Pluckthuns' invention requires mutagenesis of the displayed polypeptide via RT-PCR and PCR error (see claims 9 and 21 above), which would encompass the mutagenic PCR techniques described by Landt et al. Furthermore, a person of skill in the art would have been motivated to use the mutagenic primers as taught by Landt et al. because Landt et al.

explicitly state that their method which employs the use of said primers is "general and rapid" (e.g., see Landt et al., abstract). Finally, a person of skill in the art would have reasonably expected to be successful because Pluckthun et al. teach that mutagenic PCR methods can be used (see above) and Landt et al. state that their method can be "generally" applied (e.g., see Landt et al., abstract).

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
November 9, 2004